REMARKS

The undersigned thanks Examiner Vu for the courtesy of the telephonic interview granted on March 23, 2009. The cited art was discussed and Examiner Vu clarified that the Singh reference was inadvertently entered for the alleged 35 U.S.C. § 102 rejection. The correct reference is Chen, U.S. 6,919,370.

Claims 21-67 are pending. Claims 21-42 are presently under examination; claims 43-67 stand withdrawn. Regarding the Oath/Declaration, the Applicants note that a proper Oath/Declaration was submitted on May 26, 2005; however, the document was not properly indexed by the United States Patent and Trademark Office. The document is presently listed as "Documents Submitted with 371 Application," while the Powers of Attorney are indexed as the Oath/Declaration. A courtesy copy of the as-filed Oath/Declaration is attached hereto, for the Examiner's convenience.

Claim 21 has been amended to recite that the acid:drug compound ratio ranges from 1:1 to 100:1 by weight. Support for the amendment can be found in the specification at, for example, page 9, line 38. Claim 27 has been amended to delete "chitin derivatives." The term has been replaced with chitosan. This amendment is supported by the specification at, for example, page 106, line 7. No new matter has been added.

Rejections under 35 U.S.C. § 112

Claims 21 and 27 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Withdrawal of the rejections is requested in light of the present amendments.

Regarding claim 21, the Office alleges that the phrase "the acid:drug compound ratio is at least 1:1 by weight" is unclear. The Applicants disagree and assert that one skilled in the art would readily understand that "the acid:drug compound ratio is at least 1:1 by weight" means that the weight amount of acid is equal to or greater than the amount of drug. Nevertheless, in order to advance prosecution, the claim has been amended to recite that the acid:drug compound ratio ranges from 1:1 to 100:1 by weight. The rejection is considered moot.

Regarding claim 27, "chitin derivatives" has been replaced with "chitosan." The rejection is considered moot.

Rejection under 35 U.S.C. § 102

Claims 21-29, 31, 32, and 34-42 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by U.S. 6,919,370 (Chen). The applicants disagree and request withdrawal of the rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). MPEP 2131. "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Moreover, for those claim limitations expressly described by the reference, the Office must establish that the reference "direct[s] those skilled in the art to the [claim limitations] without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." *In re Arkley*, 455 F.2d 586,587-88 (C.C.P.A. 1972) (emphasis in original).

The present invention is directed to, among other things, ***semi-solid or solid*** pharmaceutical compositions comprising a basic drug compound, Vitamin E TPGS, and a physiologically tolerable water-soluble acid wherein the acid:drug compound ratio ranges from 1:1 to 100:1 by weight.

Chen fails to describe an identical invention in as complete detail as required by the present claims. It is only through the improper picking and choosing among the various disclosures of Chen that the Office has formulated the alleged anticipation rejection. It is the Office's burden to identify a single example in Chen that contains each and every claim limitation, arranged as in the claims. Example 11, identified by the Office as allegedly encompassing the required claim limitations, does not anticipate the claimed invention. Whereas the claimed invention requires the pharmaceutical composition to be a semi-solid or solid, Chen Formulations 1-13 are directed to ***liquid concentrate formulations***. Chen at col. 17, lines 50-51. For at least this reason, Example 11 fails to anticipate the claimed invention. Withdrawal of the rejection is requested.

Rejection under 35 U.S.C. § 103

Claims 21-42 stand rejected under 35 U.S.C § 103 as allegedly obvious over WO 01/22938 (Verreck) in view of Chen and WO 97/02017 (Clancy). The Applicants disagree and request withdrawal of the rejection.

The Office acknowledges that Verreck fails to teach using vitamin E TPGS. The Office further acknowledges that Verreck fails to teach the acid:drug ratio presently claimed.

The Applicants assert that the claimed invention would not have been obvious to one of skill in the art. As an initial matter, the Applicants reiterate that the disclosure of Chen is focused on liquid formulations, not the solid or semi-solid formulations of the present invention. As such, one skilled in the art would not have looked to Chen to modify Verreck to produce the claimed invention.

Moreover, the combination of cited art fails to suggest that the combination of a basic drug compound, Vitamin E TPGS, and a physiologically tolerable water-soluble acid wherein the acid:drug compound ratio ranges from 1:1 to 100:1 by weight, would lead to a pharmaceutical composition having the advantageous extent and stability of supersaturation, and oral bioavailability profiles of the compositions of the present invention.

Submitted herewith is a copy of an article published by the inventors of the present application and directed to compositions of the claimed invention. R. Vandecruys, et al., *Use of a screening method to determine excipients which optimize the extent and stability of supersaturated drug solutions and application of this system to solid formulation design*, Int'l J. Pharmaceutics 342 (2007) 168-175 ("Vandecruys"). As set forth therein, for drug candidates having very poor solubility, it is desirable to formulate the drug such that it will achieve supersaturation long enough for significant absorption to take place. *See* Vandecruys at 169, col. 1-2. Formulations of basic drug compounds of the invention, employing Vitamin E TPGS and a water soluble acid, exhibit supersaturation to a much greater extent than those formulations that do not include Vitamin E TPGS. *See, e.g.,* Table 2. The Applicants note that this effect is general for a range of basic drug compounds of differing molecular weights, TPSA, log P, pKa, and molecular volume. *See* Table 1; *See also*, Brewster Declaration at ¶4. The supersaturation advantage of TPGS over, for example, Cremophor RH40 and

Polysorbate 20 is unexpected and could not have been deduced from the cited art. Brewster Declaration at ¶4.

Moreover, the supersaturations obtained with formulations employing Vitamin E TPGS are more stable than for those formulations not including Vitamin E TPGS. Vandecruys at Table 3. The stability effect of TPGS over, for example, Cremophor RH40 and Polysorbate 20, is unexpected and could not have been deduced from the cited art. Brewster Declaration at ¶5.

In addition, the incorporation of Vitamin E TPGS results in a significant increase in oral bioavailability over those formulations not including Vitamin E TPGS. As set forth in Table 5 and discussed at page 174, the Vitamin E TPGS formulation exhibited a bioavailability of about 100%. Other formulations not including Vitamin E TPGS exhibited bioavailabilities of only about 30% - 60%. The superior oral bioavailability of formulations including TPGS over formulations including, for example, Cremophor RH40, is unexpected and could not have been deduced from the cited art. Brewster Declaration at ¶6-7.

The foregoing observations are further confirmed in M. Brewster, et al. *Comparative interaction of 2-hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin with itraconazole: Phase-solubility behaviour and stabilization of supersaturated drug solutions* Eur. J. Pharma. Sci. 34 (2008) 94-103 ("Brewster," attached hereto). The Applicants direct the Office to pages 99-100 and Table 1 wherein the superior effects of Vitamin E TPGS on the extent and stability of supersaturation are detailed. *See also*, Brewster Declaration at 8.

The formulations of the present invention demonstrate supersaturation, stability, and oral bioavilability profiles that are unexpected and that could not have been predicted by the cited art. As such, the claimed invention is non-obvious over the art and withdrawal of the rejection is requested.

The Applicants assert that the foregoing constitutes a full and complete reply to the March 17, 2009 Office Action and that claims 21-42 are in condition for allowance. An early notice to that effect is, therefore, earnestly solicited.

Date: September 16, 2009

/Stephanie A. Barbosa/
Stephanie A. Barbosa
Registration No. 51,430

Woodcock Washburn LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439